Supporting Information

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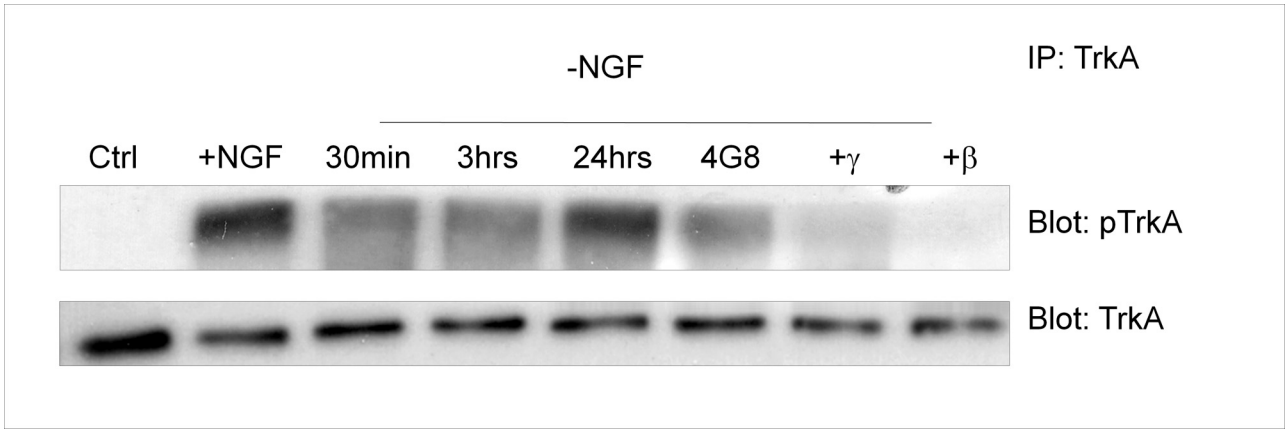
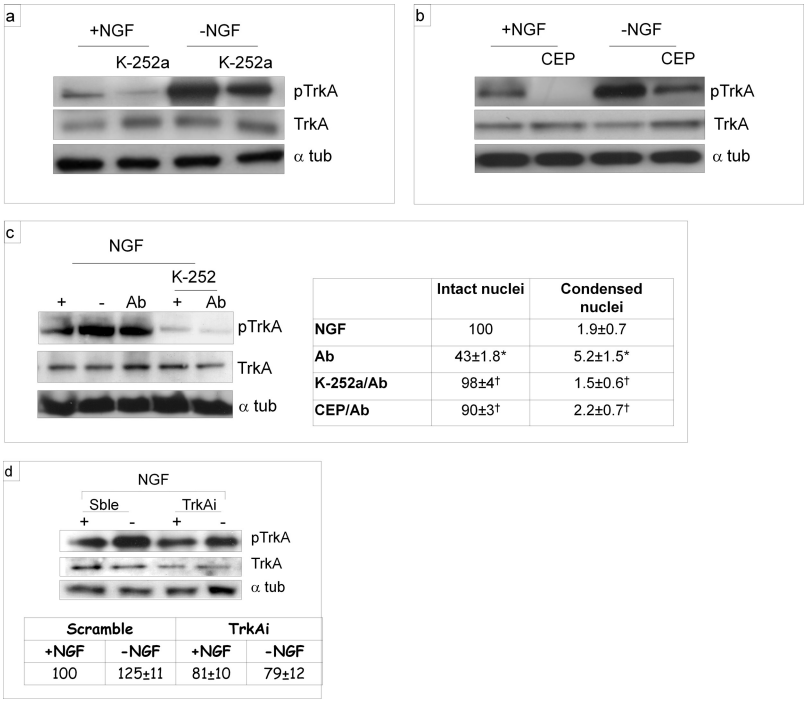


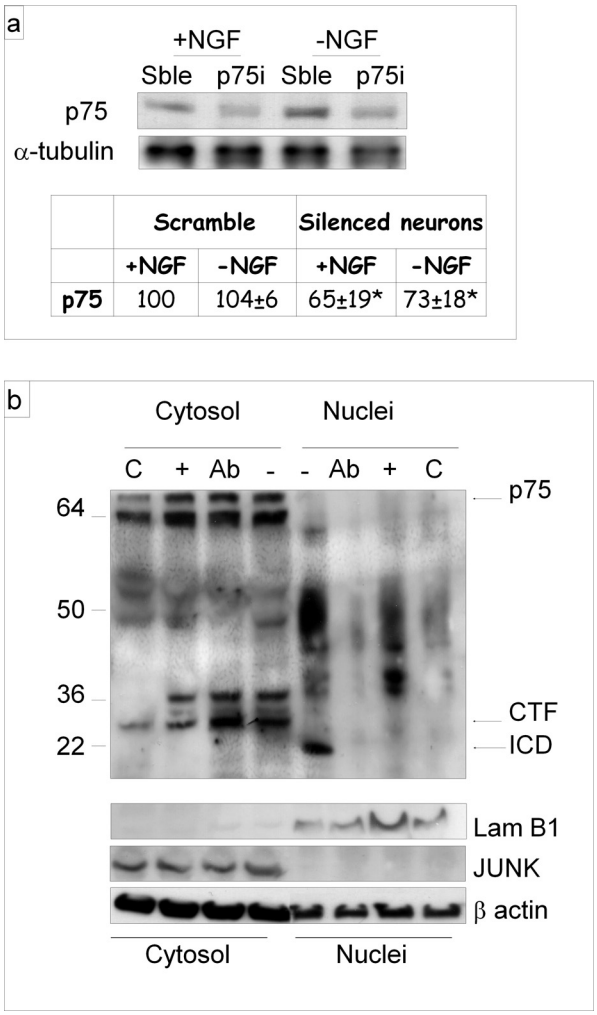
Fig. S1. Immunoprecipitation analysis of TrkA performed with a specific anti-TrkA (see *Methods*) followed by immunoblotting with TrkA(pY490) antibodies. Ctrl, hippocampal neurons before NGF exposure; +NGF, hippocampal neurons exposed to NGF; -NGF, hippocampal neurons deprived of NGF in a time ranging from 30 min to 24 h in the presence or not of anti-Abeta antibodies (4G8) or of γ and β secretase inhibitors.



	Intact nuclei	Condensed nuclei
NGF	100	1.9±0.7
Ab	43±1.8*	5.2±1.5*
K-252a/Ab	98±4†	1.5±0.6†
CEP/Ab	90±3†	2.2±0.7†

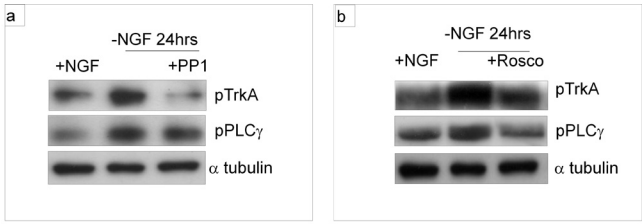
Scramble		TrkAi	
+NGF	-NGF	+NGF	-NGF
100	125±11	81±10	79±12

Fig. S2. (*a* and *b*) Western blot analysis of pTrkA after exposure to K-252a (100 nM) and CEP-2563 (200 nM), in the presence (K-252a; CEP) or not of NGF (K-252a/-NGF; CEP/-NGF). Western blots are representative of 4 different experiments. (*c*) Western blot of pTrkA in samples exposed to 10 μM Abeta 1–42 peptides (Ab) in the presence or absence of K-252a and CEP-2563 (K-252a/Ab; CEP/Ab). The corresponding extents of cell survival (evaluated as number of condensed and intact nuclei) are reported in the *Table*. Condensed nuclei are expressed as the mean ± SE of 10 fields of duplicate determinations of 5 independent experiments. Intact nuclei are reported as percentage of controls (+NGF). *$P < 0.05$ vs. cell survival of +NGF samples; †$P < 0.05$ vs. cell survival of -NGF or Abeta samples. (*d*) Western blot analysis of TrkA receptor extent after neuronal silencing (TrkAi) and of the corresponding scramble samples (Sble) in the presence (+NGF) or not (-NGF) of NGF. Western blots are representative of 4 different experiments. Optical density analysis is reported in the *Table*.



	Scramble		Silenced neurons	
	+NGF	-NGF	+NGF	-NGF
p75	100	104±6	65±19*	73±18*

Fig. S3. (*a*) Western blot analysis of p75 receptor extent after neuronal silencing (p75i) and of the corresponding scramble samples (Sble) in the presence (+NGF) or not (-NGF) of NGF. Western blots are representative of 5 different experiments. Optical density analysis is reported in the *Table*. (*b*) Cytosolic and nuclear fractions Western blot analysis performed with p75 C-terminus antibody (see *Methods*) after Abeta 1–42 (Ab) exposure (see *Methods*). C, neurons before NGF exposure; +, neurons after NGF exposure; Ab, neurons exposed to Abeta 1–42.



CELL SURVIVAL		
	Intact nuclei	Condensed nuclei
+NGF	100	2.7±0.6
-NGF	49±3*	5.7±1.8*
-NGF/+PP1	98±2.3†	2.5±0.9†
-NGF/+Rosco	87±2†	2.2±0.6†

Fig. S4. Cell survival analysis of neurons (evaluated as intact and condensed nuclei) exposed to the Src family inhibitor PP1 (1 μM) and the CDK inhibitor roscovitine (20 μM) after 24 h of NGF removal (*Table*). Values are the mean ± SE of triplicate determinations of 5 independent experiments and are expressed as percentage of control cells (+NGF). *$P < 0.05$ vs. +NGF; †$P < 0.05$ vs. -NGF samples. (*a* and *b*) pTrkA and pPLCγ Western blot analyses of the corresponding samples.

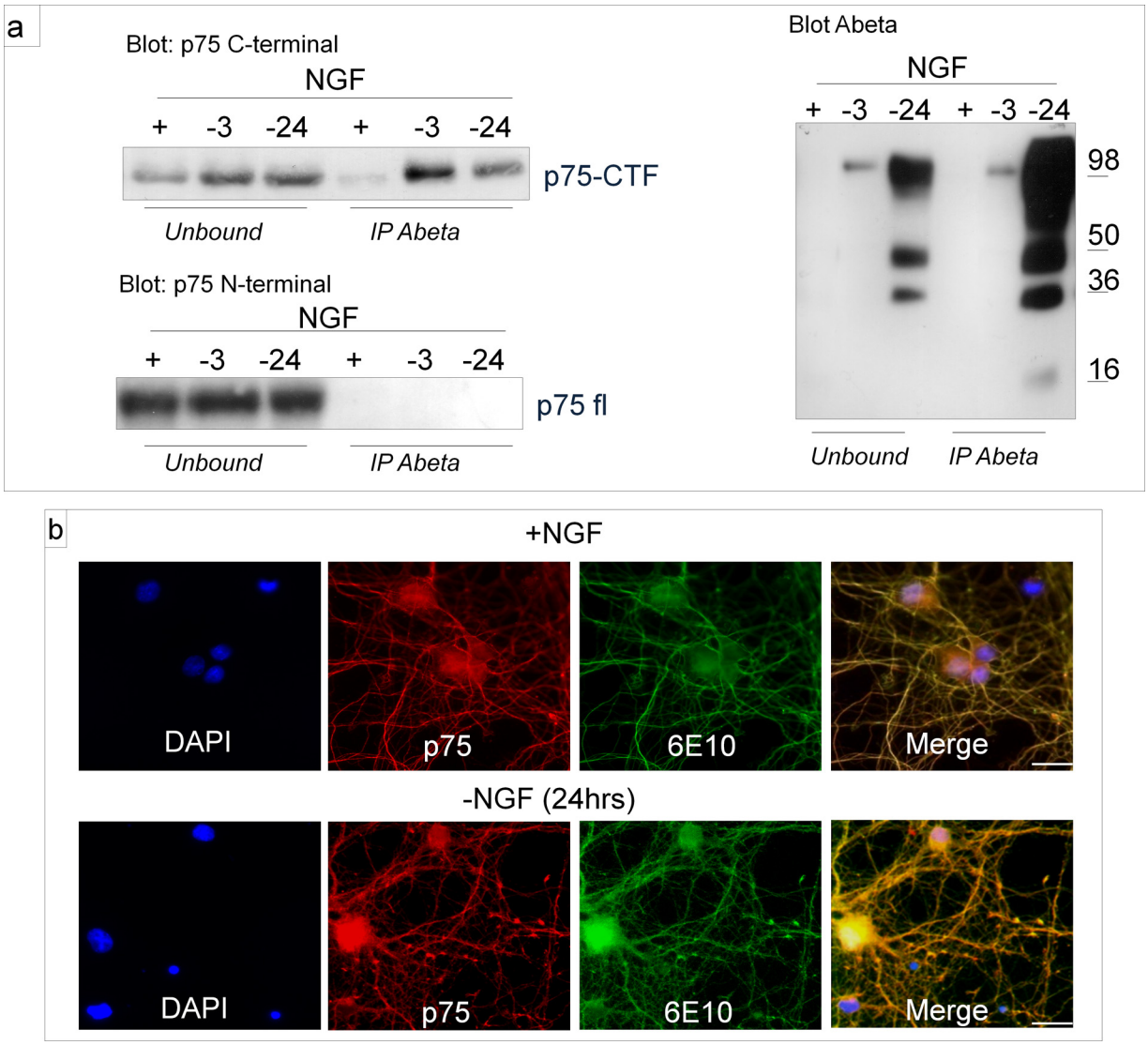


Fig. S5. (*a*) Immunoprecipitation analysis performed with anti-Abeta (see *Methods*) and blotted with p75 C-terminal antibodies (see *Methods*) from control samples (+NGF) and deprived of NGF for 3 h and 24 h (*Left*). The same samples loaded in equal amounts and run on a different gel were analyzed for Abeta antibody (Mab 6E10), confirming the binding between β-amyloid peptides and p75 (*Right*). Membranes, after stripping, were reprobed with p75 N-terminal antibody (*Bottom*) as control of loading gel. (*b*) Double-immunofluorescence performed with anti-p75 C-terminal (p75, red) and anti-Abeta antibodies (6E10, green) in the presence of NGF (+NGF) and after 24 h of NGF removal [-NGF (24hrs)]. Nuclei are stained with DAPI (blue). The corresponding merges are shown in the right-most panels. (Scale bar, 25 μm.)

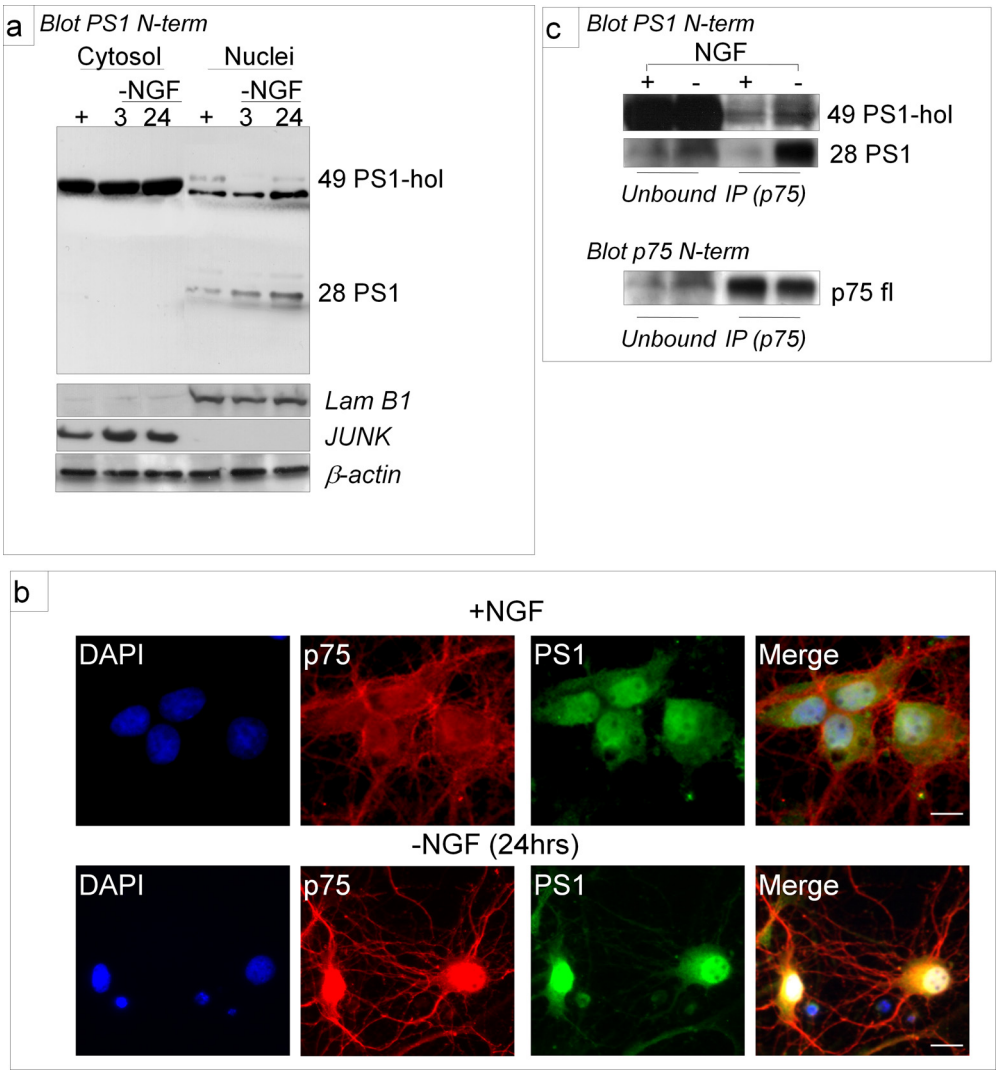


Fig. S6. (*a*) Western blot analysis of PS1 N-terminal fragments in cytosolic and nuclear fraction from samples deprived of NGF for 3 h and 24 h. PS1 hol, PS1 holoprotein (49 kDa); 28 PS1, 28-kDa PS1 N-terminus fragment. The same extracts were analyzed for JUNK and Lamin B1 (Lam B1) protein expression to determine the purity of cytosol and nuclei. Beta-actin level is shown as loading control. (*b*) Double-immunofluorescence performed with anti-p75 C-terminal (p75, red) and anti-PS1 N-terminus (green) in the presence of NGF (+NGF) and after 24 h of NGF removal [(-NGF (24 hrs)]. Nuclei are stained with DAPI (blue). The corresponding merges are reported in the right-most panels. (Scale bar, 13 μm.) (*c*) Immunoprecipitation analysis performed with anti-p75 C-terminal (see *Methods*) from control samples and after 24 h of NGF deprivation. Immunocomplexes were analyzed by immunoblotting with PS1 N-terminus antibody. At short Western blot exposure time (*Bottom*), only the 28-kDa PS1 band is present in p75 C-terminal immunoprecipitated fraction after 24 h of NGF deprivation, but longer exposure time also allows detection of the holoprotein PS1 band (*Top*). The amount of p75 brought down by the immunoprecipitation procedure was analyzed, after stripping, by blotting with p75 N-terminal antibody.

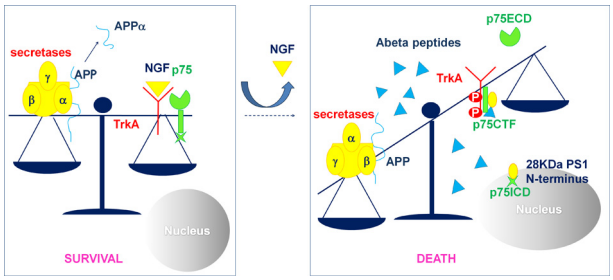


Fig. S7. After NGF removal an ''imbalance'' in NGF receptor and the APP processing systems occurs. When NGF is present and bound to TrkA, the amyloidogenic pathway is kept under control (*Left*). After NGF removal (*Right*) the balance is shifted to the amyloidogenic pathway with an unexpected TrkA phosphorylation and APP/p75 processing, to produce Abeta and p75 CTF/ICD fragments. CTF accumulates into the cytoplasm, where it associates with TrkA, Abeta peptides, and PS1 protein, whereas ICD is mainly found in the nuclear compartment, where 28-kDa PS1 N-terminus fragment is also present.

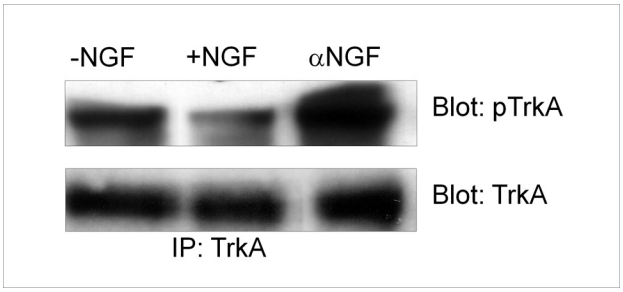


Fig. S8. Western blot analysis performed in hippocampal neurons exposed (+NGF) or deprived of NGF by simple withdrawal (-NGF) or by NGF antibody incubation (αNGF) for 24 h. Samples were immunoprecipitated with a specific anti-TrkA and immunoblotted with TrkA(pY490) antibody. The figure is representative of 3 independent experiments.